Prognostic models in cirrhosis

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Prognosis

Pro = before. Gnosis = knowledge

Prognosis = foreknowledge

A primary objective of doctors is to improve the course and outcome, i.e. the prognosis of the patient's disease.

Thus: Assessment of prognosis is an essential part of the evaluation.

Prognostication will have a significant influence on choice of therapy.

Prognostic Models

Describe the relationship between descriptive variables and an end-point, e.g. death

Empiric: Child-Turcotte score
Child-Pugh score

Statistical: Time-fixed (utilizing data at only one time)
(e.g. MELD)
Time-dependent (utilizing follow-up data)
(e.g. Copenhagen Cirrhosis Index)

Child Score

Child-Turcotte Child-Pugh

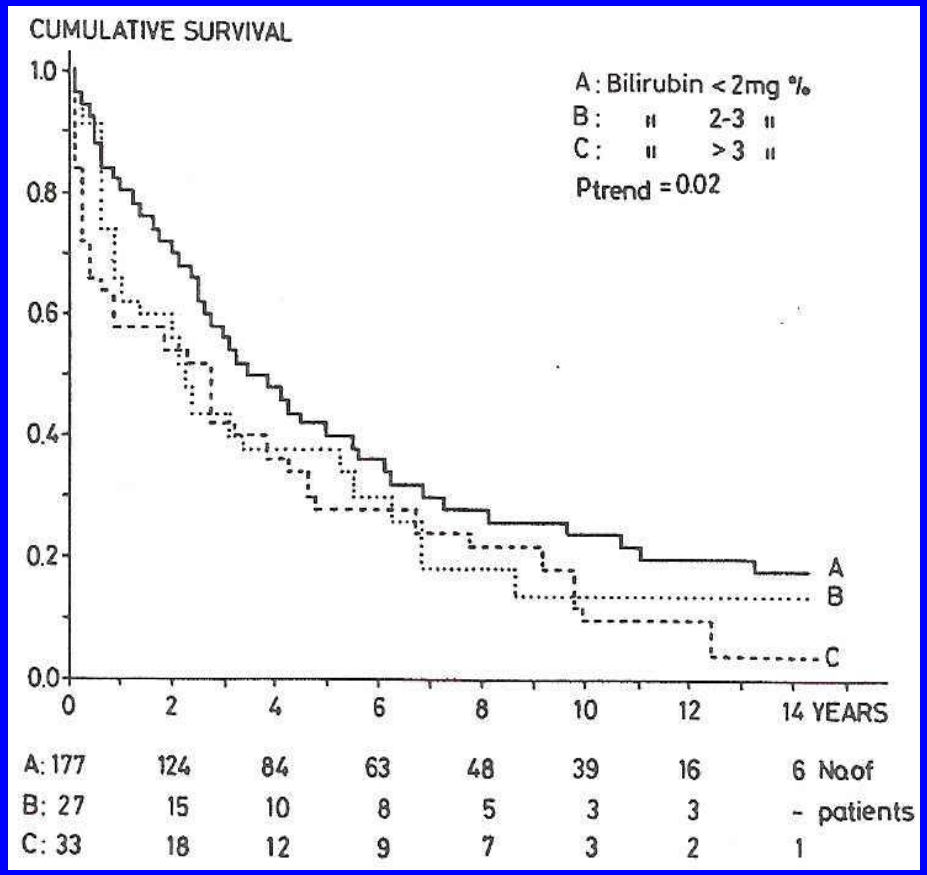
Group	A	B	C		1	2	3
Bilirubin (µmol/l)	<34	34-51	>51		<34	34-51	>51
Albumin (g/l)	>35	30-35	<30		>35	28-35	<28
Ascites	Absent	Control-led	Refrac-tory		Absent	Control-led	Refrac-tory
Encephalopathy	None	Minimal	Advanced (coma)		None	Minimal	Advanced (coma)
Nutritional Status	Good	Fair	Poor		-	-	-
Prothrombin	-	-	-		<4 s >50%	4-6 s 38-50%	>6 s <38%

C.G. Child and J.G. Turcotte, Surgery and portal hypertension In: C.G. Child, Editors, *The liver and portal hypertension*, W. B. Saunders Co., Philadelphia (1964), p. 50.

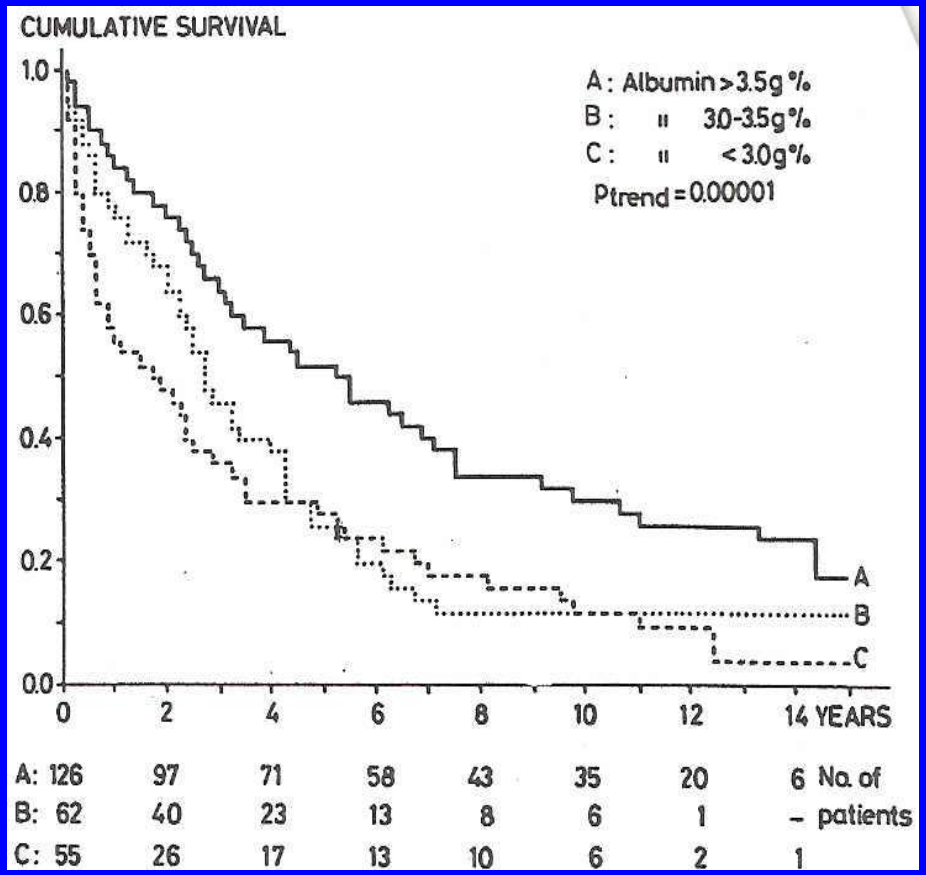
R.N. Pugh, I.M. Murray-Lyon, J.L. Dawson, M.C. Pietroni and R. Williams, Transection of the oesophagus for bleeding oesophageal varices, *Br J Surg* 1973; 60 : 646–9.

Prognostic influence of single variables

Bilirubin

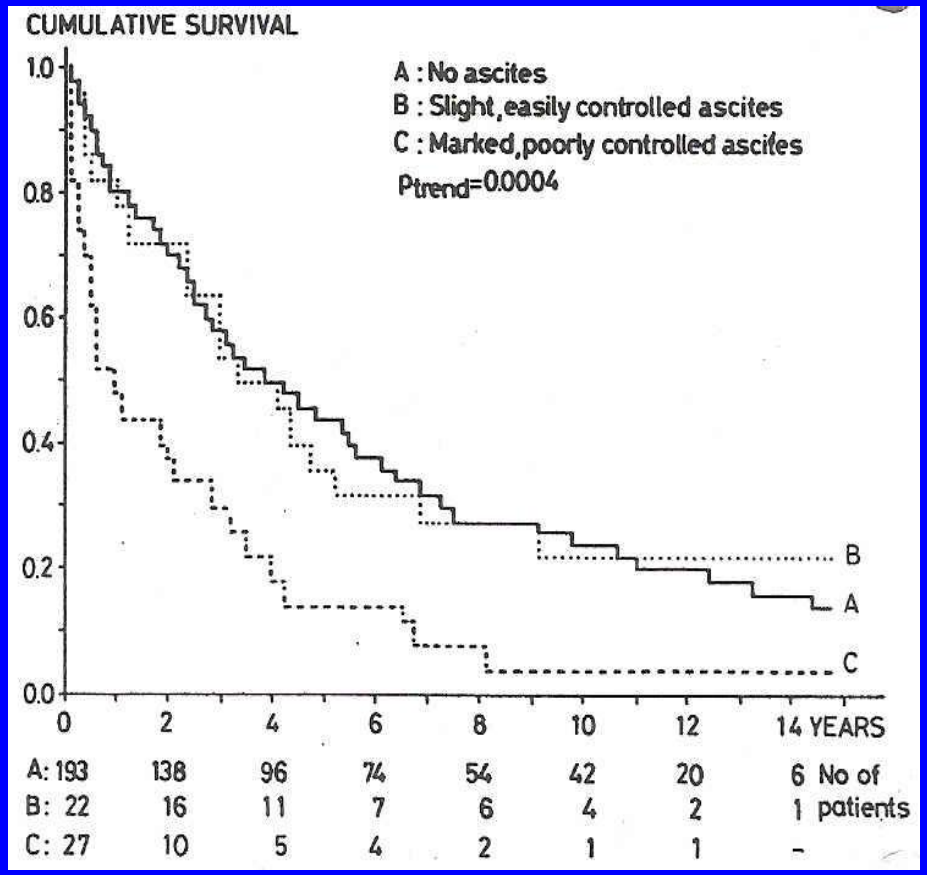


Albumin

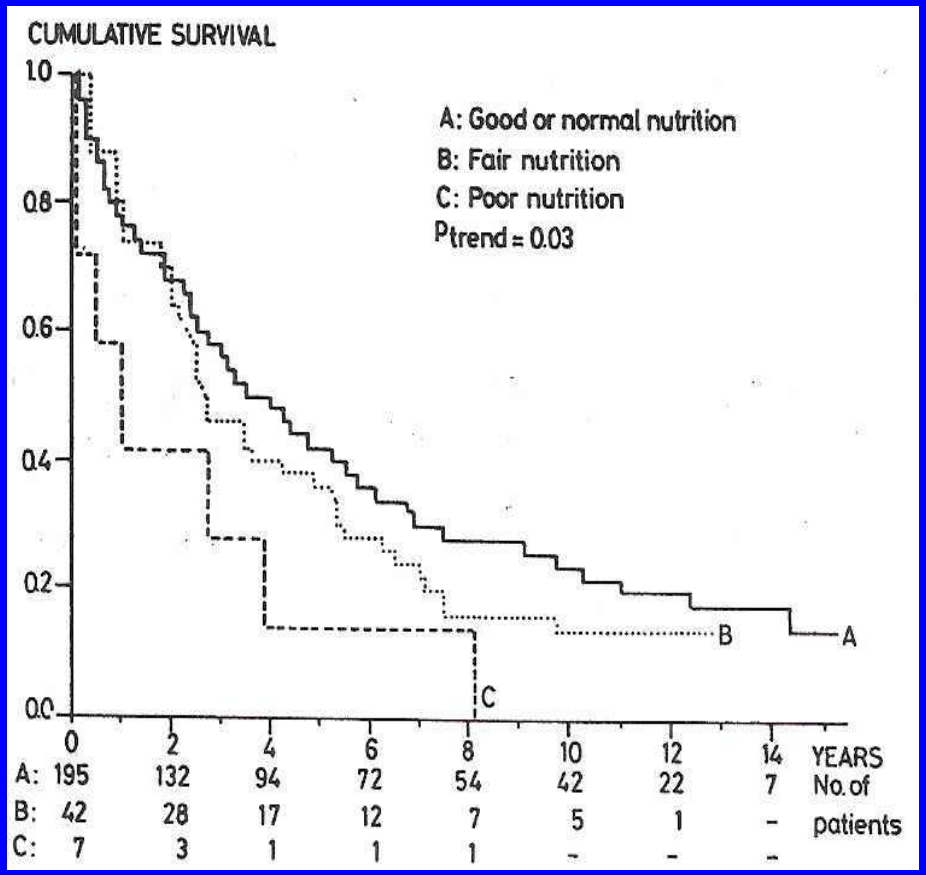


Prognostic influence of single variables

Ascites

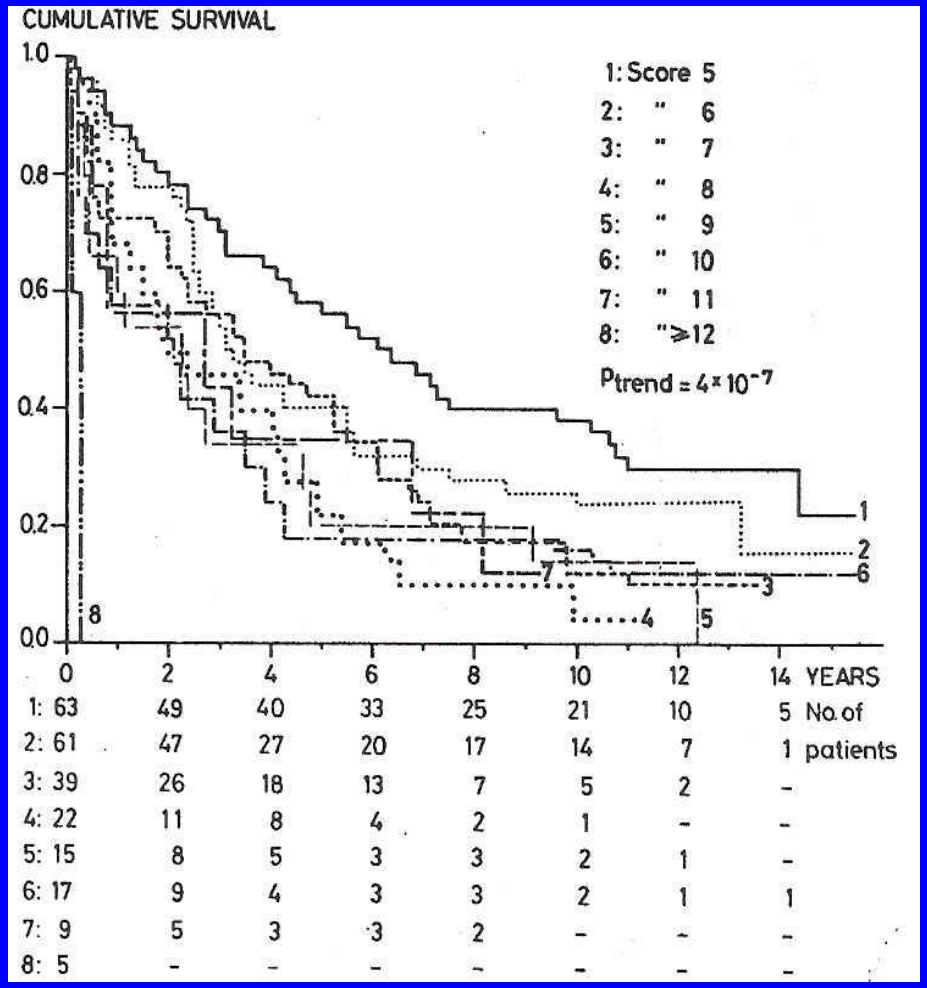


Nutrition

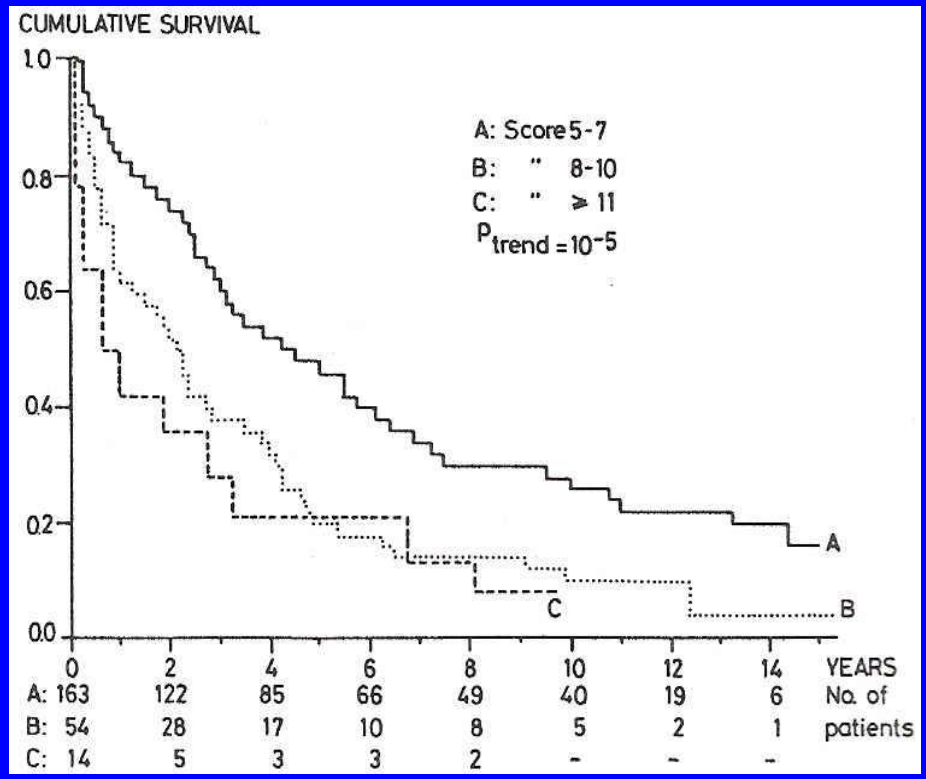


Prognostic influence of Child-Turcotte score (combined variables)

Full score



Score in groups



Child-Turcotte / Child-Pugh score

Advantages:

- Simple to use
- Variables easy to obtain
- Does hold some prognostic information

Disadvantages:

- Use of cut-off points for quantitative variables reduces the prognostic information
- The cut-off points used for the variables are not optimal
- The five variables used are not equally important
- The points allocated for each variable are not additive
- Some variables (ascites, encephalopathy, nutritional status) are open to some interpretation
- Some important variables (e.g. Age, gastro-esophageal varices, variceal bleeding and serum creatinine) are not included
- Relation between score and survival probability not explicitly defined

MELD score
Model for End-stage Liver Disease

$$R = 0.957 \times \log_e(\text{creatinine [mg/dl]}) + 0.378 \times \log_e(\text{bilirubin [mg/dl]}) + 1.120 \times \log_e(\text{INR}) + 0.643 \times \text{cirrhosis type [alcoholic or cholestatic: 1, other: 0]}$$

$$S(t) = S_0(t)^{\exp(R - 1.127)}$$

Days:	1	7	30	90	183	365	730
$S_0(t)$:	0.990	0.966	0.860	0.707	0.621	0.551	0.428

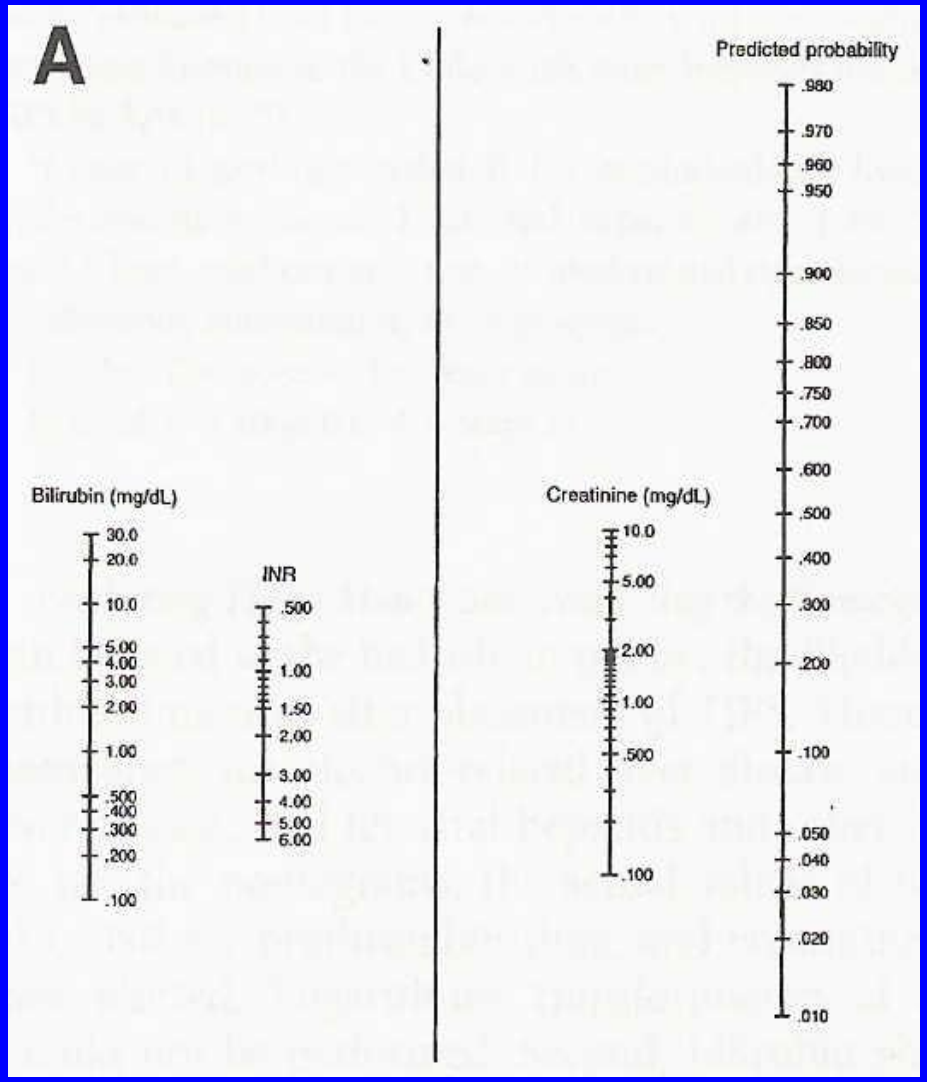
M. Malinchoc, P.S. Kamath, F.D. Gordon, C.J. Peine, J. Rank and P.C.J. Ter Borg, A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; 31: 864–71.

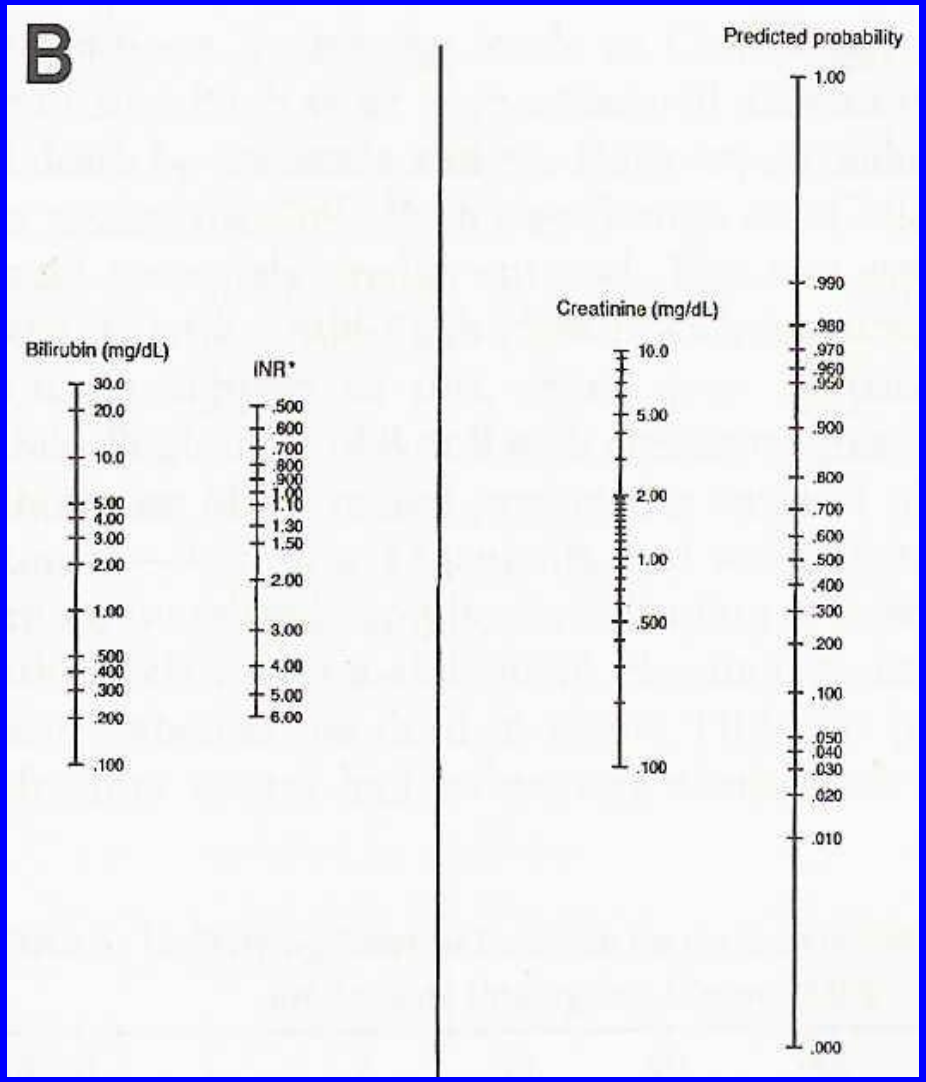
MELD nomogram: 3 months probability of death

Hepatology 2000; 31: 864–71.

Alcoholic or cholestatic cirrhosis

Other type of cirrhosis





Using MELD nomogram - example

Patient with alcoholic cirrhosis

Bilirubin: 5 mg/dL

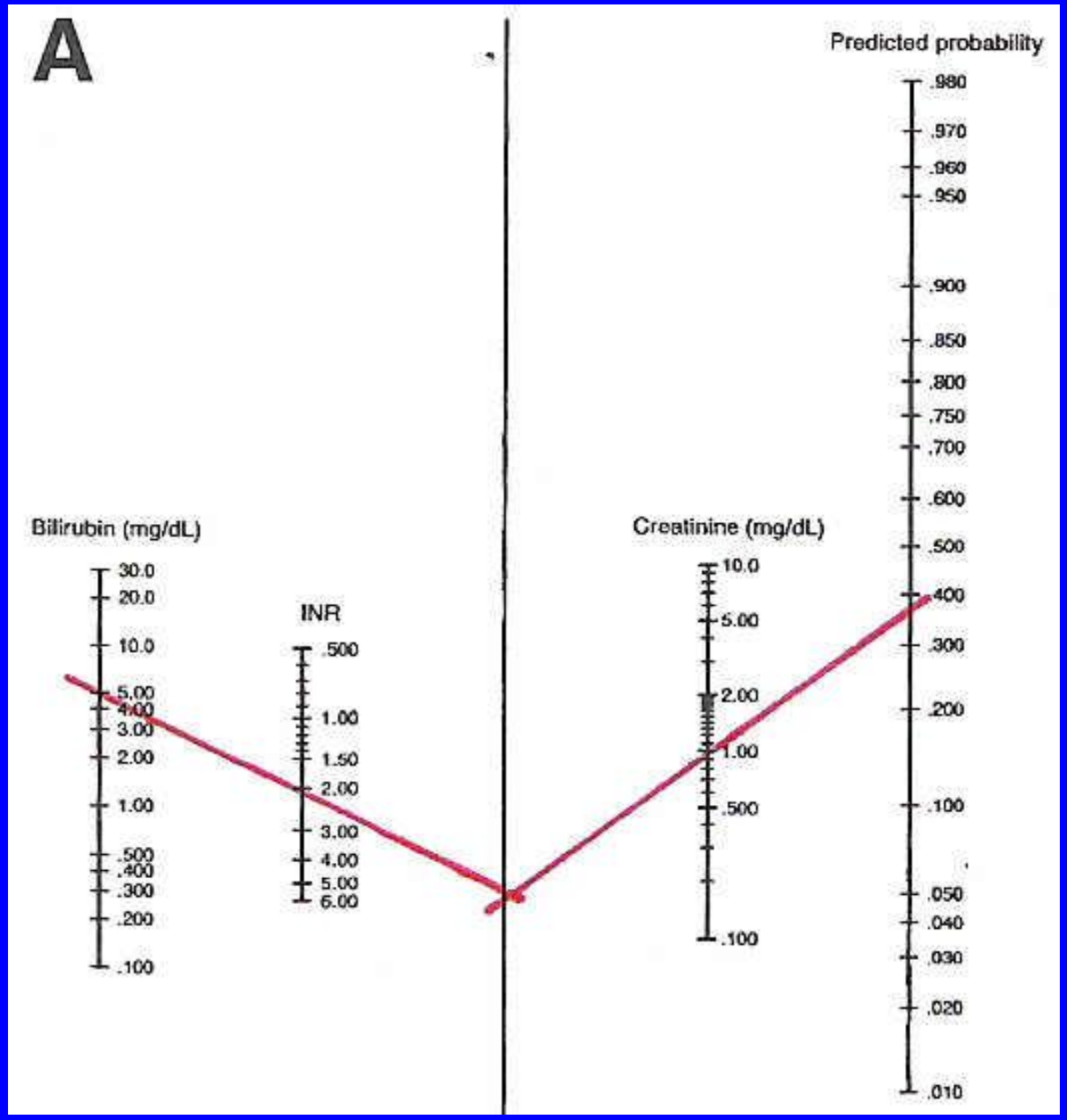
INR (International normalized ratio): 2.0

Creatinine: 1 mg/dL

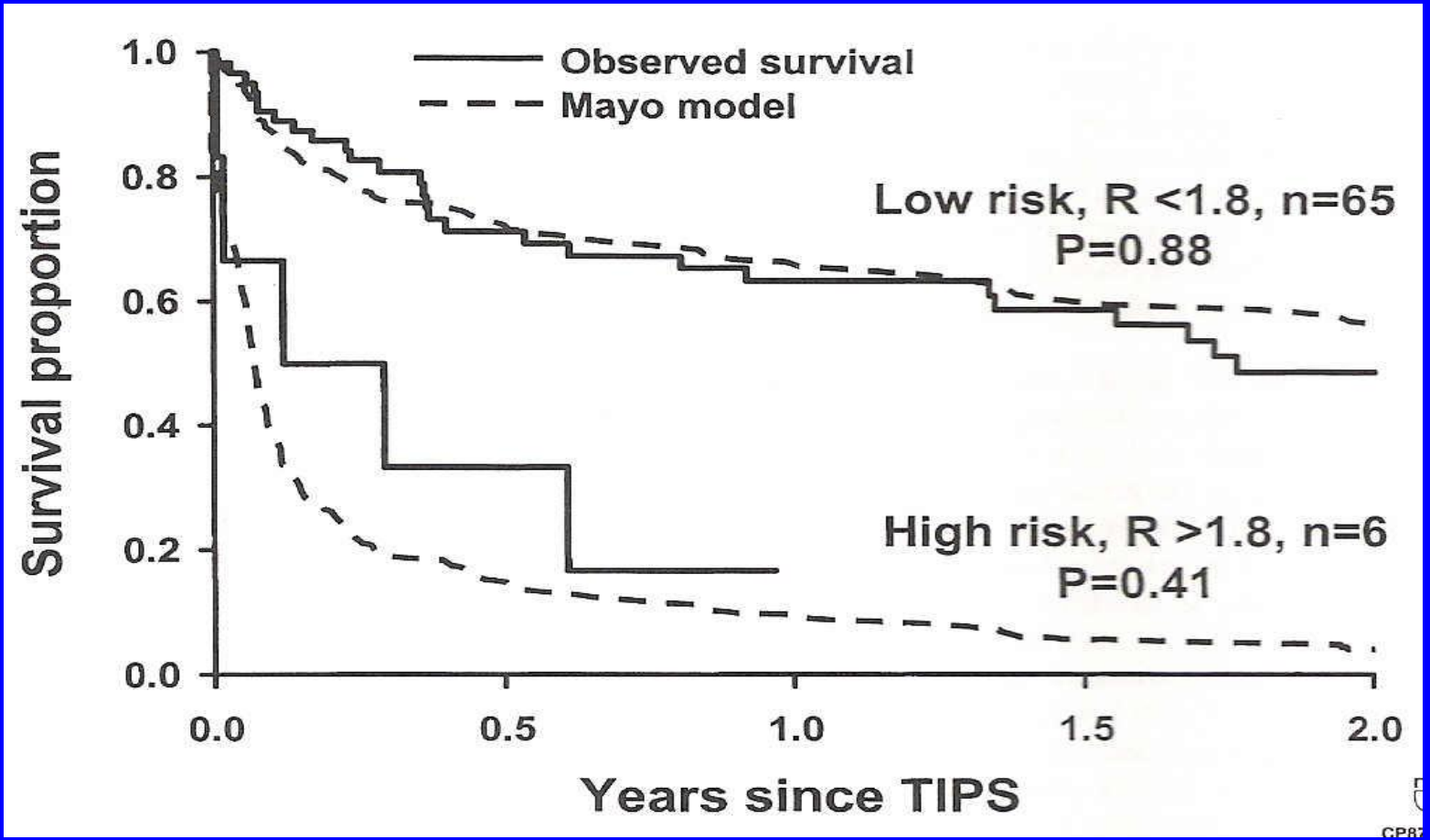
Probability of death within 3 months:

<u>About 0.36 or 36%</u>

(Hepatology 2000; 31: 864–71.)



Validation of MELD score in independent patients



Hepatology 2000; 31: 864–71.

MELD score

Advantages:

- Statistically sound
- Useful irrespective of specific diagnosis
- Variables objective

Disadvantages:

- Some important variables may be missing:
  e.g. ascites, encephalopathy, albumin, age,
  oesophageal varices, variceal bleeding
  Some of these were significant in univariate analysis,
  but did not contribute significantly ($p<0.01$) in the model
  (type 2 error?).
- Slightly difficult to calculate

Prognostic accuracy measured by concordance (*c*) statistic (1.0 is perfect and 0.5 is random)

Number of patients	Mortality	Child-Pugh	MELD
637	1 month	0.71-0.78	0.72-0.73
4493	3 months	0.67-0.84	0.70-0.87
766	1 year	0.66-0.74	0.66-0.73
1611	3 years	0.83	0.79

Can follow-up data be utilized?

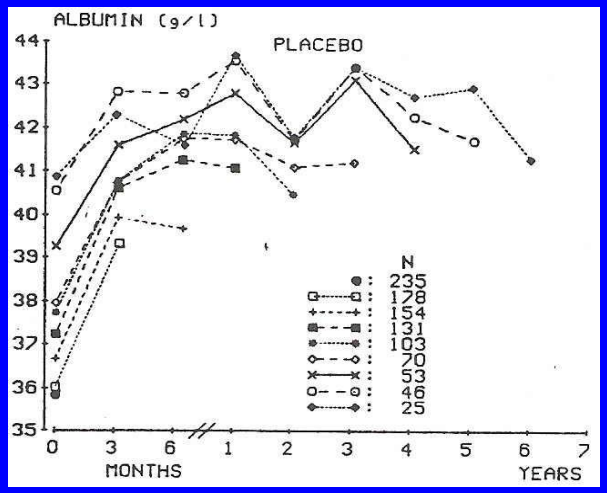
Prognosis is not fixed

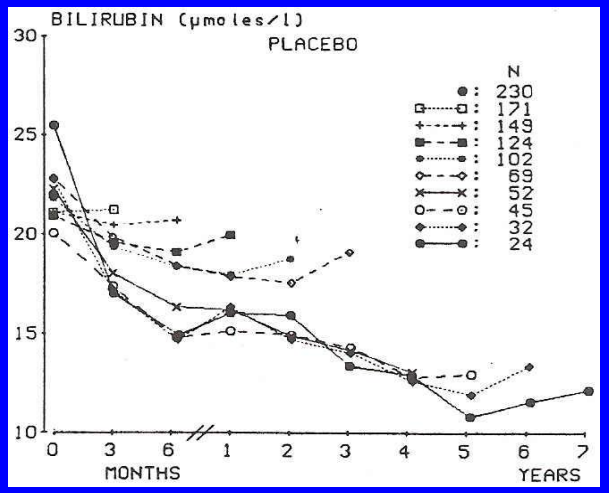
It *changes with time* dependent on

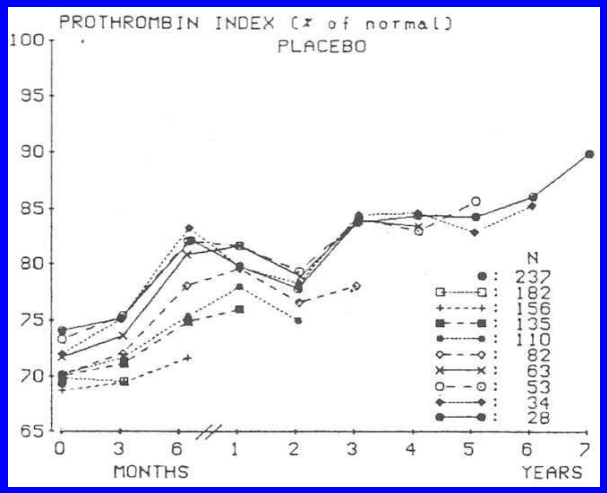
- The underlying disease activity
- Occurrence of complications
- The effect of therapy

By utilizing follow-up data in the development of the prognostic model, it can be used to update prognosis during the course of the disease.

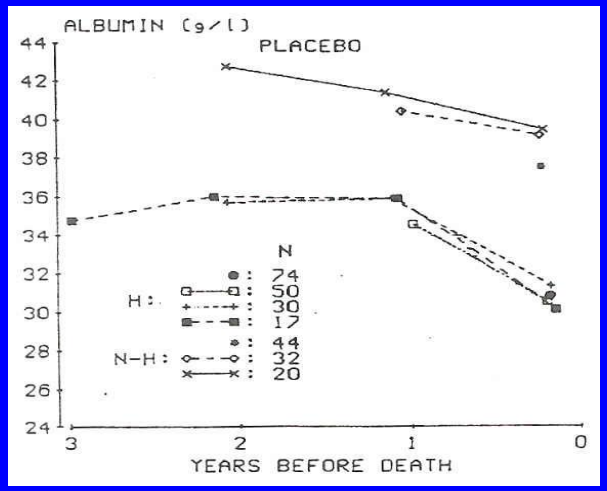
Time course of variables **after diagnosis**

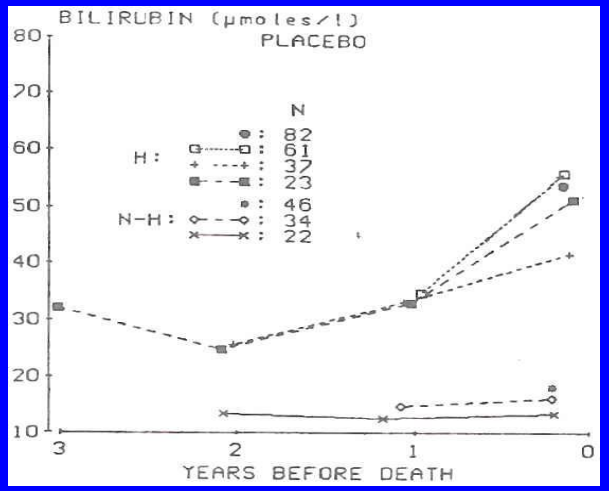


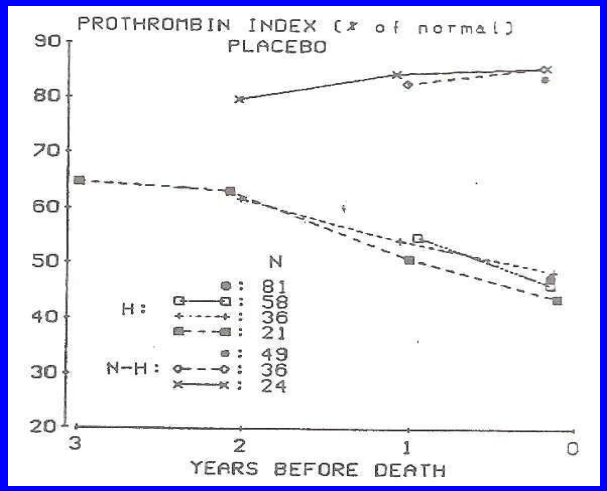




Time course of variables **prior to death**







E. Christensen, P. Schlichting, L. Fauerholdt *et al.*, Changes of laboratory variables with time in cirrhosis: prognostic and therapeutic significance. *Hepatology* 1985; **5** : 843–53.

Copenhagen time-dependent prognostic index in cirrhosis - based on 3603 sets of data at different time points

Pocket chart for calculation of current prognostic index in cirrhosis

Variable			Points to add
Age (years)		20	0
		30	5
		40	11
		50	16
		60	21
		70	26
		80	31
Current alcohol consumption	none		0
	10–50 g/day		4
	>50 g/day		13
Ascites	none		0
	slight		3
	moderate or marked		12
GI bleeding		no	0
		yes	14
Nutritional status	normal or fat		0
	meagre or cachectic		6
Serum bilirubin	<4 mg/100 ml or <70 μmol/l		0
	≥4 mg/100 ml or ≥70 μmol/l		9

Serum albumin	g/l	μmol/l	
	15	228	14
	20	304	10
	30	456	6
	40	608	2
	50	760	−1
Prothrombin index (% of normal)		10	22
		15	19
		20	16
		30	13
		40	11
		55	8
		70	6
		105	3
		150	0
Alkaline phosphatase (IU/l)		37	0
		70	2
		107	4
		180	6
		290	8
		400	10
Liver connective tissue inflammation			
	Unknown		0
	None or slight		4
	Moderate or marked		−2
Sum of points S=			
Prognostic index PI(t)=S/10−6=.			

From: E. Christensen, Prognostic models in chronic liver disease: validity, usefulness and future role. *J Hepatol* 1997;26: 1414–24 and *Scand J Gastroenterol* 1986 ; 21 : 163–74.

Copenhagen time-dependent prognostic index in cirrhosis - Example

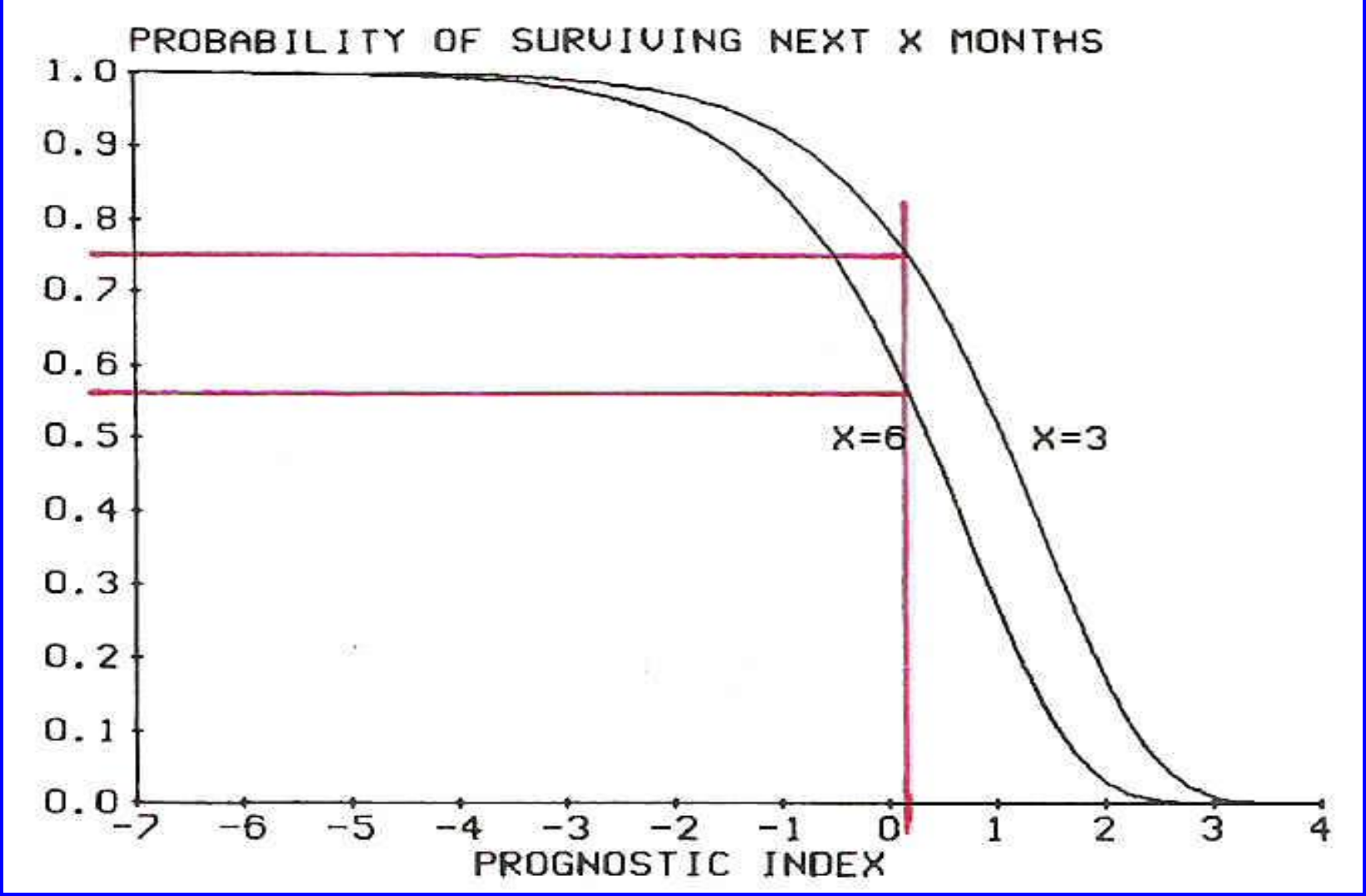
Pocket chart for calculation of current prognostic index in cirrhosis

Variable			Points to add	
Age (years)		20	0	
		30	5	
		40	11	
	54	50	16	18
		60	21	
		70	26	
		80	31	
Current alcohol consumption	none		0	
	10–50 g/day	30g/d	4	4
	>50 g/day		13	
Ascites	none		0	
	slight		3	
	moderate or marked		12	12
GI bleeding		no	0	0
		yes	14	
Nutritional status	normal or fat		0	
	meagre or cachectic		6	6
Serum bilirubin	<4 mg/100 ml or <70 µmol/l	35 µmol/l	0	0
	≥4 mg/100 ml or ≥70 µmol/l		9	

Serum albumin	g/l		µmol/l		
	15		228	14	
	20	420 µmol/l	304	10	7
	30		456	6	
	40		608	2	
	50		760	−1	
Prothrombin index (% of normal)			10	22	
			15	19	
			20	16	
			30	13	
		45	40	11	10
			55	8	
			70	6	
			105	3	
			150	0	
Alkaline phosphatase (IU/l)			37	0	
			70	2	
		139 IU/l	107	4	5
			180	6	
			290	8	
			400	10	
Liver connective tissue inflammation					
	Unknown			0	0
	None or slight			4	
	Moderate or marked			−2	
Sum of points S=					62
Prognostic index PI(t)=S/10−6=.		6.2−6=			0.2

J Hepatol 1997;26: 1414–24 and *Scand J Gastroenterol* 1986 ; 21 : 163–74.

Copenhagen prognostic index in cirrhosis
Calculation of survival probability



J Hepatol 1997;26: 1414–24 and *Scand J Gastroenterol* 1986 ; 21 : 163–74.

Other time-dependent prognostic models

Primary biliary cirrhosis (PBC)

- Royal Free Model (age, bilirubin, albumin and history of ascites)

  (*Stat Med* 1992;11:1731-45)

- European model (age, bilirubin, albumin, ascites, GI bleeding, IgM)

  (*Gastroenterology* 1993; **105** : 1865–76.)

- Mayo model (age, bilirubin, albumin, prothrombin time and edema)

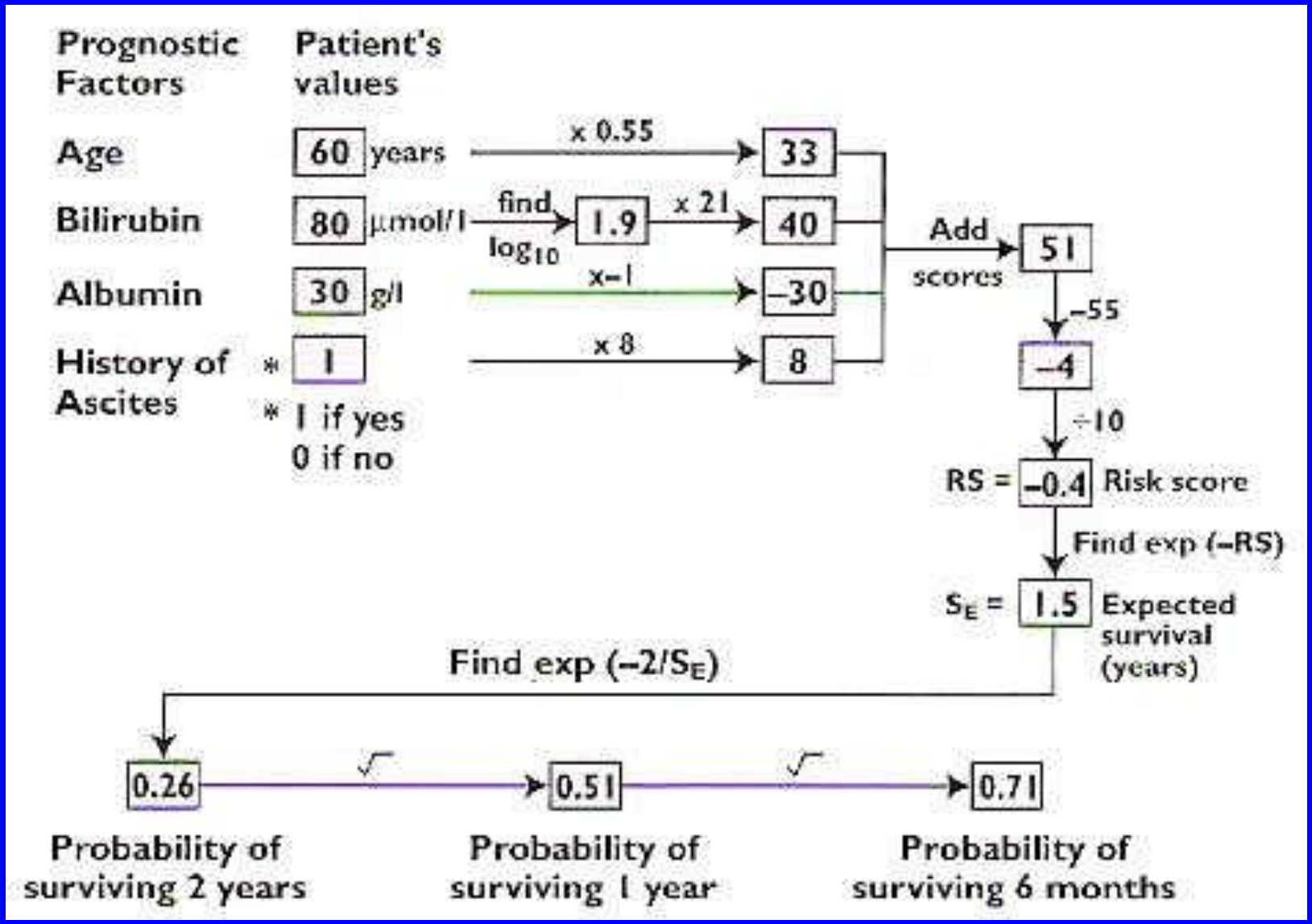
  (*Hepatology* 1994; 20: 126–34.)

Primary sclerosing cholangitis (PSC)

- European model (age at diagnosis, bilirubin, albumin)

  (*Hepatology* 2002; **35** : 652–57.)

Royal Free time-dependent prognostic model for PBC – Pocket chart example



Stat Med 1992;11:1731-45

Coefficients of Mayo models for PBC

Variable	Time-fixed	Time-dependent
Age (years)	0.039	0.051
Log_e bilirubin (mg/dl)	0.871	1.209
Log_e prothrombin time (sec)	2.380	2.754
Log_e albumin (gm/dl)	-2.533	-3.304
Edema score (0, 0.5 or 1)	0.859	0.675

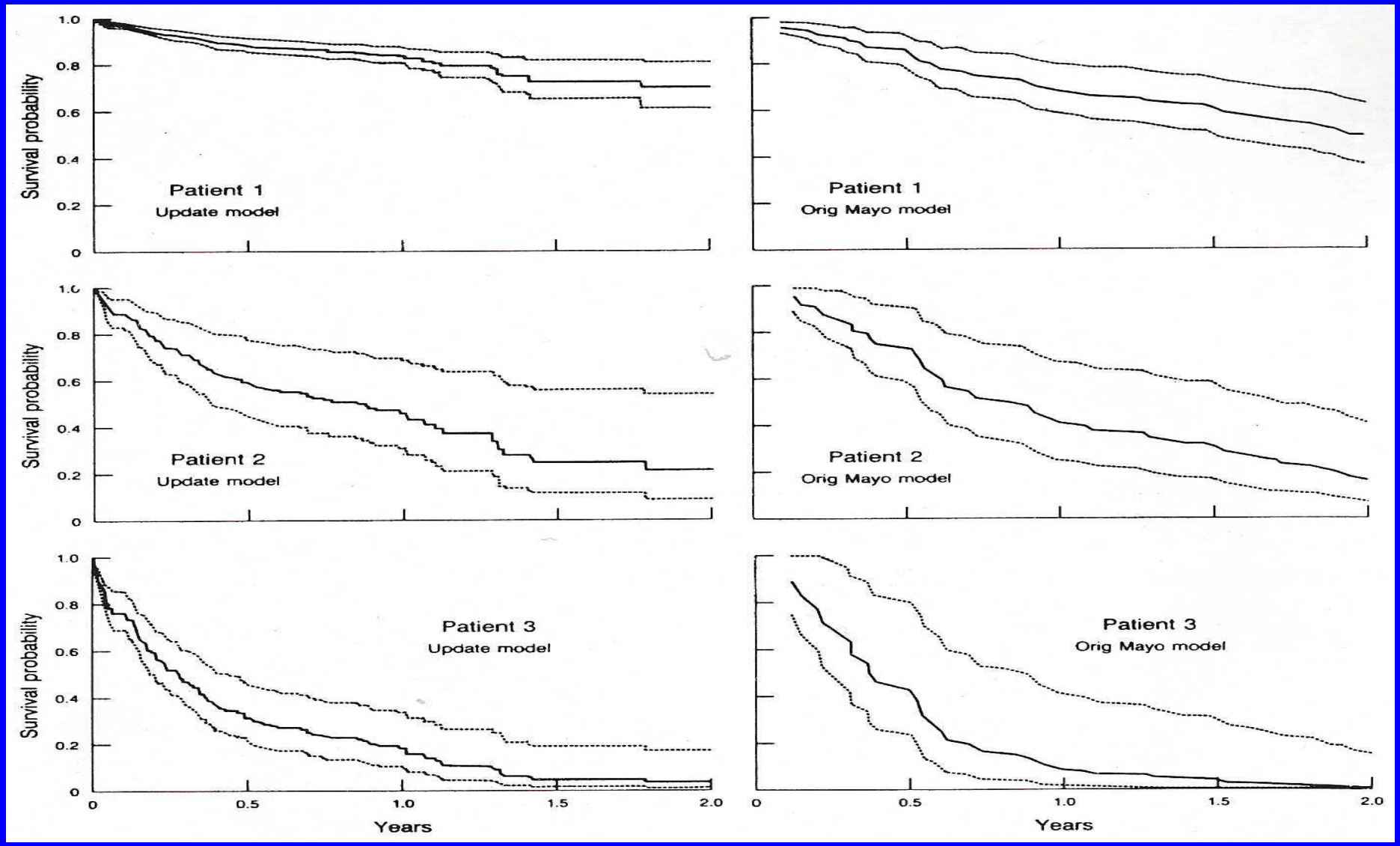
Hepatology 1989;10:1–7. Hepatology 1994;20;126–34.

Coefficients tend to be numerically *larger* in the time-dependent model
The prognostic follow-up information is also utilized

95% confidence limits: Mayo model for PBC

Time-dependent model

Time-fixed model



Hepatology 1994;**20;**126–34.

Hepatology 1989;10:1–7.

Prognostic estimates are not precise

- 95% confidence intervals of survival probability estimates are wide!
- In general only 10 – 45% of the variation of survival in the model data is ”explained” by prognostic models.
- Prognostication will be poorer in independent patients.

Why are prognostic models not precise?

- Weakly informative descriptive variables
  (peripheral to the real problem)
- We use too few variable recordings
- Variables interact in a complex fashion
  (linear models may be too simple)
- Important variables still unknown

Clinical use of prognostic models

- Facilitated by using ”pocket charts” and diagrams
- Provide *guidance* to the prognosis of individual patients
- Estimate change in short term prognosis (time-dependent models)
- Timing of liver transplantation (time-dependent models)
- Improved description (and comparison) of patient groups (average and distribution of prognostic indices)
- Illuminate and inspire pathogenetic studies
- Educational value for students and untrained doctors

How can we improve prognostic models?

We need to include follow-up data to a greater extent in the prognostic modelling.

We need to develop models from larger combined data bases from various centres.

We need better prognostic variables that are central to the disease process. Hopefully, gene technology and molecular biology will increase our knowledge in this respect.